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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,425	02/12/2002	Kent D. Taylor	P-CE 5187	8130

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,425	TAYLOR ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4/2002* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejection - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-2 and 4-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing or predicting susceptibility to Crohn's disease in an individual comprising detecting the presence or absence in said individual of a 2-2-4 haplotype at the Notch 4, HSP70-HOM and D2S273 loci, wherein the presence of said haplotype is diagnostic of or predictive of susceptibility to Crohn's disease in said individual, does not reasonably provide enablement for a method of diagnosing or predicting susceptibility to any autoimmune disease by detecting the presence of the 2-2-4 haplotype or a method of diagnosis or predicting susceptibility to Crohn's disease by detecting a disease associated haplotype or an allele "associated" with the 2-2-4 haplotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples,

(4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to diagnosing or predicting the susceptibility to *any* autoimmune disease associated with the 2-2-4 haplotype in any individual by detecting the presence or absence of a 2-2-4 haplotype at the Notch 4, HSP70-HOM and D6S273 loci. The claims are further drawn to diagnosing or predicting the susceptibility of rheumatoid arthritis, or Type I diabetes, or Crohn's disease, or inflammatory bowel disease in any individual by detecting the presence or absence of a 2-2-4 haplotype at the Notch 4, HSP70-HOM and D6S273 loci. The claims are further drawn to a method of diagnosis or predicting susceptibility to Crohn's disease by detecting a disease associated haplotype "associated" or an allele "associated" with the 2-2-4 haplotype.

The amount of direction or guidance:

The specification teaches that the Notch 4 gene is a member of the Notch gene family which is located near the centromeric end of the MHC class III locus on chromosome 6. The specification teaches that the Notch 4 gene has 7 alleles corresponding to different numbers of tandem repeat of the trinucleotide (CTG) located in exon 1 of the gene. The specification teaches that the "2" allele corresponds to a 325 base pair fragment (pp 6-7). With regard to the HSP70-HOM locus and the D6s273 microsatellite marker, the specification teaches that the HSP70 proteins are indicated in immune response and that the "2" allele corresponds to a T at position 2437 of the HSP70-HOM gene. The specification teaches that the D6S273 locus is a

microsatellite polymorphism that is located at nucleotides 34073 to 34114 and that this locus has 7 alleles, the "4" allele corresponding to a 134 bp fragment. The specification teaches how to detect each allele of the 2-2-4 haplotype (see page 30).

The specification does not teach the function of any genes at this locus, nor how the alleles are involved in any of the diseases claimed.

Presence and absence of working examples:

The specification teaches of a study which was composed of 108 patients with CD and 69 ethnically matched control subjects (mainly spouses) who were genotyped (p. 28). The specification teaches that in family studies, an association was found between the Notch4 2 allele and CD (p=.011). The specification teaches that the association increased with detecting of the 2-2 alleles (Notch4 and HSP70-HOM) and the 2-2-4 alleles (Notch4, HSP70-HOM, and D6S273) (p=0.0044 and p=0.00097, respectively, see pages 32-33). In a case control panel, the specification teaches that the association between the 2-2-4 haplotype and Crohn's disease was stronger than with the Notch4 allele alone (see page 33).

With regard to claims 1-12, the specification provides no working examples of an association between the 2-2-4 haplotype and the broad scope of the diseases encompassed by "autoimmune disease".

With regard to claims 13-20, the specification provides no working examples of any association between Crohn's disease and a) the presence or absence of a "disease associated haplotype associated with the 2-2-4 haplotype" or b) "a disease associated allele associated with the 2-2-4 haplotype". Additionally, the specification demonstrates at figure 3 that the

combination of the HSP70-HOM allele 2 and the D6S273 allele 4 are not associated with Crohns disease (p=0.22). The specification teaches that a "disease associated haplotype associated with the 2-2-4 haplotype" and "a disease associated allele associated with the 2-2-4 haplotype" are haplotypes or alleles that are inherited more often than would be expected according to traditional Mendelian genetics. While the specification provides examples of a few alleles that 'could' be contained within a 'disease associated haplotype" or "a disease associated allele", the specification provides no guidance or examples as to any specific haplotype "associated with" the 2-2-4 haplotype nor does the specification teach how tightly linked the alleles, which are suggested to be associated, are with the 2-2-4 haplotype. It is clear from the teachings of figure 3, for example, that MHC alleles, just by virtue of being MHC alleles, are not predictably associated with Crohn's disease. Additionally, it is clear from the teachings in the specification, that 'disease associated haplotypes and alleles' are population specific. For example, at page 31, the specification teaches that previous reports found an association between HLA-DRB*0103 and CD, but that such association was observed in non Jews, whereas the teachings in the study taught by the specification, which involved an Ashkenazi Jewish population, did not find an association with CD and that therefore the observations in the specification were not due to linkage disequilibrium between Notch4 and HLA-DRB1. Therefore, while the specification has shown an association between CD and the 2 allele of Notch4, as well as the 2-2-4 haplotype for Notch4, HSP70-HOM, and D6S273, the specification has provided no correlation that an allele in linkage disequilibrium with any of these alleles or haplotype would be predictably associated with Crohn's disease, or any autoimmune disease in general.

The state of the prior art and the predictability or unpredictability of the art:

An association with the claimed haplotype and any autoimmune disease, or any inflammatory bowel disease (IBD), such as ulcerative colitis (UC), based on data only obtained with patients with Crohn's disease (CD) is clearly unpredictable given the state of the art. Rector et al (Genes and Immunity, vol. 2, pp 323-328, October 2001) teach that inflammatory bowel diseases (IBD) in general, as well as CD and UC are complex multifactorial traits involving both environmental and genetic factors (see abstract). Rector teaches that a study of point mutations in codons 52, 54, and 57 of exon 1 of mannan-binding lectin, which plays an important role in non specific immunity, were significantly lower in frequency in UC patients when compared with CD patients. Lesage et al (American Journal of Human Genetics, vol 70, pp 845-857, 2002) teaches that CARD15/NOD2 encodes a protein involved in bacterial recognition by monocytes and that mutations in CARD15 have been associated with CD. Lesage teaches that an analysis of 3 polymorphisms which were independently associated with susceptibility to CD were not associated to UC (see abstract). Further, Over et al (European Journal of Gastroenterology and Hepatology, vol. 10, pp 827-829, 1998) teaches that a study that tested the frequency of a point mutation in factor V (FV Leiden), which has been identified in various thromboembolic diseases, found that FV Leiden was found to be statistically more frequent in CD patients but not in UC patients (see abstract). Thus, as exemplified by the state of the art regarding polymorphisms in genes or genetic markers and their association with IBD's, an association between specific polymorphisms or mutations and any IBD, such as UC, based on an association with such to CD, is unpredictable. Although polymorphisms in some genes have been linked to both CD and UC, a large number of polymorphisms are also associated to only one disease and not the other, as

exemplified by the cited art. Therefore, the art does not provide the skilled artisan with a predictable correlation that polymorphisms, markers, or specific haplotypes linked to CD are also linked to any IBD, such as UC.

An association with the claimed haplotype and either rheumatoid arthritis (RA) and type I diabetes mellitus (IDDM) is also unpredictable as exemplified by the state of the art. For example, Singal et al (Tissue Antigens, vol. 52, pages 353-358; 1998, see page 355) teaches that only the D6S273 allele 132 and 138 bp alleles are associated with RA. Additionally, Kim et al (Tissue Antigens, vol. 54, pages 552-559, 1999) teaches that there was no significant difference between RA and controls in D6S273 alleles (see abstract). Also, Steer et al (Rheumatology, vol. 43, pages 304-307, 2003) demonstrates that two polymorphisms in the CARD15 gene, which were found to contribute to CD disease risk, did not show any significant association to RA (see abstract and page 306. As such, Steer et al question whether CARD15 is in fact a common autoimmune susceptibility locus. Also of note, Herbon et al (Genomics, vol. 81, pages 510-518; 2003) exemplifies that polymorphisms which are associated with CD, are not necessarily associated with IDDM (see table 1, SNP #4). Thus, as exemplified by the state of the art regarding polymorphisms in genes or susceptibility markers and their association with CD, an association between specific polymorphisms or mutations and any autoimmune disease such as RA or IDDM based on an association with such to CD, is unpredictable. Although polymorphisms in some genes have been linked to both CD and RA or other autoimmune diseases, a large number of polymorphisms or markers are also associated to only one disease and not the other, as exemplified by the cited art. Therefore, the art does not provide the skilled

artisan with a predictable correlation that polymorphisms linked to CD are also predictably linked to any autoimmune disease such as RA or IDDM.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

To practice the invention as claimed, the skilled artisan would have to perform a large study of patients with different types of diseases such as UC, RA, and IDDM, and matched controls to determine if the polymorphism claimed was associated with any autoimmune disease. Such a study would consist of mainly trial and error analysis, the outcome of which is clearly unpredictable as exemplified by the state of the art. Given the lack of guidance from the specification as to any statistical association between the claimed haplotype and any autoimmune disease other than CD, such as UC, RA, or IDDM, and the unpredictability taught in the art as to an association between polymorphisms or markers associated with both CD and UC, RA, or IDDM for example, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it is claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of working examples directed to the broad scope of the claims and the negative teachings in the art balanced only against the high skill level in the art, it is the position

of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Written Description

3. Claims 13-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13-20 are broadly drawn to a method of diagnosis or predicting susceptibility to Crohn's disease by detecting a disease associated haplotype "associated" or an allele "associated" with the 2-2-4 haplotype. The genus of alleles or haplotypes is very large, and includes uncharacterized haplotypes and alleles from a large portion of the genome.

The specification teaches how to detect each allele of the 2-2-4 haplotype (see page 30). The specification teaches of a study which was composed of 108 patients with CD and 69 ethnically matched control subjects (mainly spouses) who were genotyped (p. 28). The specification teaches that in family studies, an association was found between the Notch4 2 allele and CD (p=.011). The specification teaches that the association increased with detecting of the 2-2 alleles (Notch4 and HSP70-HOM) and the 2-2-4 alleles (Notch4, HSP70-HOM, and D6S273) (p=0.0044 and p=0.00097, respectively, see pages 32-33). In a case control panel, the specification teaches that the association between the 2-2-4 haplotype and Crohn's disease was stronger than with the Notch4 allele alone (see page 33).

However, the specification provides no description or examples of any association between Crohn's disease and a) the presence or absence of a "disease associated haplotype associated with the 2-2-4 haplotype" or b) "a disease associated allele associated with the 2-2-4 haplotype". Additionally, the specification demonstrates at figure 3 that the combination of the HSP70-HOM allele 2 and the D6S273 allele 4 are not associated with Crohns disease (p=0.22). The specification teaches that a "disease associated haplotype associated with the 2-2-4 haplotype" and "a disease associated allele associated with the 2-2-4 haplotype" are haplotypes or alleles that are inherited more often than would be expected according to traditional Mendelian genetics. While the specification provides examples of a few alleles that 'could' be contained within a 'disease associated haplotype" or "a disease associated allele", the specification provides no guidance or examples as to any specific haplotype "associated with" the 2-2-4 haplotype nor does the specification teach how tightly linked the alleles, which are suggested to be associated, are with the 2-2-4 haplotype. It is clear from the teachings of figure 3, for example, that MHC alleles, just by virtue of being MHC alleles, are not predictably associated with Crohn's disease. Additionally, it is clear from the teachings in the specification, that 'disease associated haplotypes and alleles' are population specific. For example, at page 31, the specification teaches that previous reports found an association between HLA-DRB*0103 and CD, but that such association was observed in non Jews, whereas the teachings in the study taught by the specification, which involved an Ashkenazi Jewish population, did not find an association with CD and that therefore the observations in the specification were not due to linkage disequilibrium between Notch4 and HLA-DRB1. Therefore, while the specification has shown an association between CD and the 2 allele of Notch4, as well as the 2-2-4 haplotype for

Notch4, HSP70-HOM, and D6S273, the specification has not demonstrated that an allele in linkage disequilibrium with any of these alleles or haplotype would be predictably associated with Crohn's disease, or any autoimmune disease in general, nor has the specific described any specific haplotype or allele which is associated with CD and the 2-2-4 haplotype.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). With the exception of the 2-2-4 haplotype, the skilled artisan cannot envision the detailed chemical structure of the encompassed haplotypes or alleles in the genus claimed.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-3 and 5-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,376,176.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the broader claims of the instant application (ie genus) are obvious over the more specific (species) claims of the '176 application. For example, the instant claims are drawn to diagnosing or predicting susceptibility to any autoimmune disease by detecting a specific haplotype whereas the claims are more narrowly drawn to detecting Crohn's disease by detecting the same specific haplotype. Additionally, the instant claims are broadly drawn to detection in any individual, whereas the claims of the '176 application are limited to detection in Ashkenazi Jewish individual. The courts have stated that a genus is obvious in view of the teaching of a species. See Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); and In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

Conclusion

6. No claims are allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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Art Unit 1634
9/28/04